The biological role of epithelial-mesenchymal transition in lung cancer (Review)

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Abstract. Epithelial-mesenchymal transition (EMT) is a process whereby epithelial cells gradually transform into mesenchymal-like cells losing their epithelial functionality and characteristics. EMT is thought to be involved in the pathogenesis of numerous lung diseases ranging from developmental disorders and fibrotic tissue remodeling to lung cancer. Lung cancer is the most lethal form of cancer worldwide, and despite significant therapeutic improvements, the patient survival rate still remains low. Activation of EMT endows invasive and metastatic properties upon cancer cells that favor successful colonization of distal target organs. The present review provides a brief insight into the mechanism and biological assessment methods of EMT in lung cancer and summarizes the recent literature highlighting the controversial experimental data and conclusions.

Contents

1. Introduction

Epithelial-mesenchymal transition (EMT) is a process whereby epithelial cells gradually acquire a mesenchymal cell phenotype. EMT is associated with cancer progression, and is involved in its metastasis and treatment resistance as well as embryonic development and inflammatory process (1,2). During EMT, cells lose their epithelial proteins and acquire mesenchymal proteins (3). This transition allows cancer cells to gain the ability to pass through the basement membrane and achieve increased invasive ability (4-6).

Through the process of EMT, cancer cells not only lose their cell-cell adhesion of epithelial phenotype and exhibit elevated motility and invasion, but also gain increased resistance to chemotherapeutic drugs (1). In addition, activation of EMT leads to the generation of cancer cells with stem cell-like characteristics (7-10). Therefore, cancer cells undergoing EMT may become drug-resistant cancer cell progenitors, or cancer stem cells (CSCs) (11). Pulmonary stem cells were first identified at the bronchioalveolar duct junction and these cells were termed bronchioalveolar stem cells (12). In recent years, lung CSC research has gained considerable momentum for both basic and clinical applications (11).

The present review provides an overview of the EMT of lung cancer in regards to the tumor microenvironment, CSCs, related cytokines or chemical mediators, related transcription factors, EMT epigenetics, invasion/metastasis and putative therapeutic applications.

2. Tumor microenvironment and stem cells

Inflammation in the lung microenvironment contributes to tumor initiation and invasion, promoting cancer cell EMT through its ability to induce the downregulation of epithelial cell proteins and upregulation of mesenchymal cell proteins (13,14). The continuous and bilateral crosstalk, which occurs in the tumor microenvironment, is mediated by molecules secreted by either tumor or microenvironment stromal cells (15). This crosstalk of inflammatory mediators between tumors and their stroma results in tumor cell invasion, angiogenesis and metastasis (16).

Hypoxia is an essential characteristic of the tumor microenvironment (17). It promotes the developing tumor microenvironment through activation of NF-κB signaling in macrophages, neutrophils and stromal cells (18,19). Increased expression of hypoxia-related proteins are found in the central necrotic regions and the invading front of the tumor (20,21). The hypoxic microenvironment has emerged as an important

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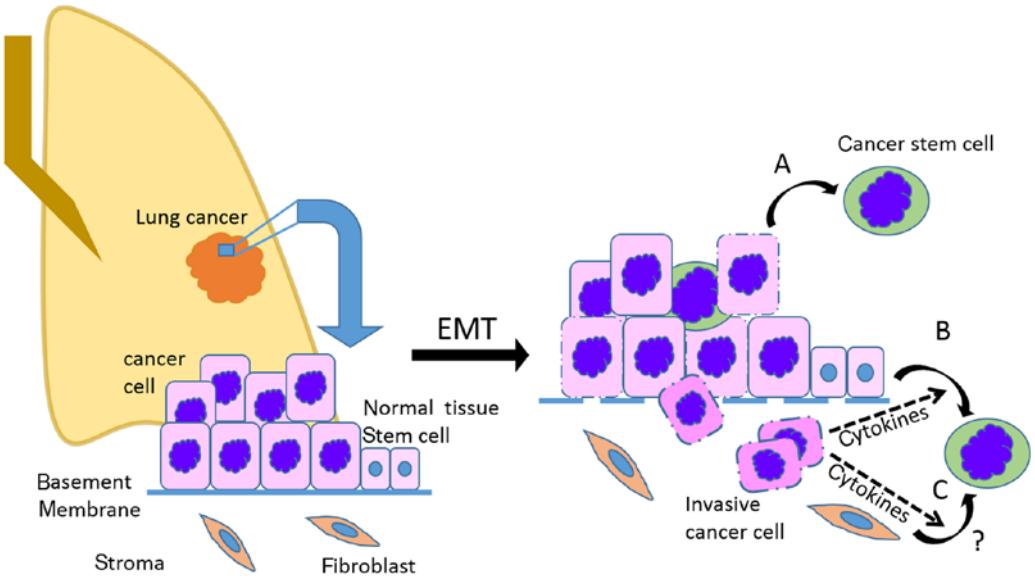

Figure 1. Cancer stem cell model. (A) Various cancer cells within the clonal tumor cell population are altered to cancer stem cells. (B) Malignant conversion of normal tissue stem cells into cancer stem cells via induction of EMT occurs in the tumor environment. (C) Fibroblasts in the tumor microenvironment are altered to cancer stem cells.

factor in the induction of EMT (17), and is associated with loss of epithelial gene expression, such as E-cadherin and induction of mesenchymal gene expression, such as fibronectin and collagen.

Carcinoma-associated fibroblasts (CAFs) are known as major components of the tumor microenvironment and are involved in cancer cell growth and survival, including angiogenesis and invasion (17). CAFs in the tumor microenvironment are present at the invasive front of the tumor (17). The conversion of fibroblasts into CAFs is driven by cancer cell-derived cytokines, such as transforming growth factor-β1 (TGF-β1) (15). CAFs produce extracellular matrix molecules and growth factors, including TGF-β, FGF2 and VEGF, leading to a conversion from a normal to a cancer-supporting microenvironment, a process known as tumor stromatogenesis (22). Bonde *et al* (23) reported that analysis of non-small cell lung cancer revealed a positive correlation between intratumoral CAF densities, EMT markers, intraepithelial TGF-β levels and tumor grade.

Numerous components of the tumor microenvironment have been associated with CSCs and carcinogenesis, suggesting that the developing tumor microenvironment drives expansion and possible malignant conversion of normal tissue stem cells into CSCs via induction of EMT (Fig. 1). The precise origin of lung CSCs still remains to be resolved, but the term CSCs refers to tumorigenic cells with the ability to self-renew and to generate the diverse cell types present within the tumor (24,25). Since most tumors are clonal in origin, tumorigenic CSCs must have the ability to give rise to a phenotypically diverse progeny (24) resulting in different degrees of proliferation, differentiation and invasiveness (26,27). It has been revealed that normal tissue stem cells and CSCs share several stem cell-associated characteristics, such as the expression of primitive stem cell markers (28).

The employment of stem cell markers remains the most widely used approach for identifying lung CSCs (11). The markers currently used to isolate lung CSCs, are CD44, CD24, CD133 and ALDH (28-30). CD44 plays an important role in tumor cells undergoing an EMT-like process and is associated with cancer progression (31,32). CD44-positive NSCLC cells were shown to be enriched in CSCs and resistant to cisplatin treatment (33). Sullivan *et al* (30) discovered that ALDH selects for a subpopulation of self-renewing NSCLC stem-like cells with increased tumorigenic potential, and NSCLC patients with ALDH1 tumor cells were found to have a worse prognosis (17). Since a single definite lung CSC marker has not yet been identified, a combination of markers are required for a reliable quantification of CSCs (11).

Through the assessment of CD133 expression, Eramo *et al* (34) managed to identify CD133-positive lung CSCs in primary human lung cancer specimens (11). These CD133-positive cells were shown to proliferate indefinitely and to display resistance to chemotherapeutic drugs. Hilbe *et al* (35) suggested that CD133-positive progenitor cells may play a role in NSCLC tumor vasculogenesis.

Several studies have investigated the potential clinical impact of lung CSC markers (11). The identification of new CSC biomarkers for diagnosis and treatment would be crucial for a better understanding of lung CSCs.

3. Chemical mediators and transcription factors in EMT

The molecular markers involved in EMT help to distinguish an epithelial cell from a mesenchymal cell. Cells undergoing EMT typically show an increase in the protein abundance of vimentin, N-cadherin, fibronectin, and a decrease in E-cadherin, cytokeratins and occludin (36).

Early molecular signs of EMT involve the dissociation of cell-cell junctions induced by downregulation or disassembly of junctional components, such as occludins, ZO-1, claudins and E-cadherin (2,4). Loss of E-cadherin expression is considered to be a hallmark of EMT (11). This loss is followed by

Table I. Transcription factors related with EMT of lung cancer.

Transcription factors	Related signaling pathways	Downregulated products	Upregulated products
Snail	Smad2/3 (TGF-β1), β-catenin (Wnt), Notch, AKT (PI3K), NF-κB, integrin, EGF, FGF	E-cadherin, claudins, occludin, cytokeratins, desmoplakin	Fibronectin, N-cadherin, collagen, MMPs, TWIST, ZEB
Slug	Integrin, EGF, FGF	E-cadherin, cytokeratin, desmoplakin, MUC-1	Fibronectin, vimentin
Twist	MAPK, NF-κB	E-cadherin, claudins, occludin, desmoplakin, plakoglobin	Fibronectin, N-cadherin, α5, integrin
ZEB	Smad2/3 (TGF-β1), β-catenin (Wnt), RAS-MAPK	E-cadherin, ZO1, Crumbs3, plakophilin	Collagen, SMA, fibronectin, N-cadherin, MMPs

EMT, epithelial-mesenchymal transition; EGF, epidermal growth factor; FGF, fibroblast growth factor; MMPs, metalloproteinases.

upregulation of several mesenchymal markers, which is associated with an increased invasive potential (37). The regulators involving mesenchymal differentiation, such as Snail and Twist, are considered to regulate the EMT-induced decrease in E-cadherin expression (38,39).

Vimentin is a widely expressed protein that is constitutively expressed in mesenchymal cells, including endothelial cells, macrophages, neutrophils, fibroblasts and leukocytes (40,41). Vimentin is a typical marker of EMT by which epithelial cells acquire a mesenchymal phenotype that causes them to alter their shape and motility (42). In normal lung tissue, vimentin expression is restricted to the basal and columnar cells of the bronchial epithelium (43). However, in lung cancer, increased vimentin expression is associated with epithelial-derived tumor cells (44), and is used as a diagnostic marker for invasive and metastatic tumor cells (45,46).

Other cytoskeletal changes involve the expression of fibroblast-specific protein (FSP) in the bronchial epithelium, which is associated with a more invasive phenotype and worse prognosis in lung cancer (47).

The Notch signaling pathway participates in the establishment of motile and invasive mesenchymal phenotypes from polarized epithelial properties, involving downregulation of epithelial markers and upregulation of mesenchymal markers (48,49). The involvement of Notch signaling in lung cancer was experimentally confirmed in a transgenic mouse model (50). Clinical studies have observed that Notch signaling impacts survival in lung cancer patients (51). A recent study by Donnem *et al* assessed the prognostic impact of Notch ligands and receptors in NSCLC and found that high Notch expression was statistically associated with poor outcomes in lung adenocarcinoma patients (52).

TGF-β1, a ubiquitous cytokine with profound growth inhibitory effects on epithelial and other tissues, orchestrates an intricate signaling network that is crucial to determine cell differentiation and proliferation, leading to not only tumor suppression but also EMT related with tumor invasion (53). TGF-β1 mediates the interaction of Smad to the promoters of Snail, contributing to the development of EMT in NSCLC (54,55). This could be blocked by pharmacological inactivation of Notch, indicating the key role of Notch signaling in TGF-β-induced EMT (56). Meanwhile, inhibition of Notch signaling significantly inhibited TGF-β1-induced expression of SMA, suggesting that Notch induces EMT through a TGF-β1-Smad pathway that activates SMA gene transcription (57).

It is well established that during the physiological repair process after injury, loosening of epithelial-epithelial cell contacts, alteration of cell-extracellular matrix contacts, and morphological changes occur during wound repair (58). These phenotypic changes are thought to be mediated by EMT transcription factors (59). Key transcription factors driving EMT in lung cancer include Snail, Slug, Twist and ZEB family (Table I), which are repressors of E-cadherin transcription.

Aberrant expression of Snail expression has been noted in lung cancer (60). Strong Snail expression is observed at the leading edges of squamous cell carcinomas with loss of E-cadherin expression, suggesting a role for Snail in migration and invasion (60). Heinrich *et al* (17) demonstrated that Snail overexpression contributed to an increase in tumor size and metastasis.

The ZEB family (ZEB1 and ZEB2), another group of transcription factors, contributes to EMT in lung cancer (61,62). Immunohistochemical study revealed that ZEB1 and Twist are commonly expressed in lung tumors (63). Downregulation of claudin 1 by Snail and Slug has been observed of lung cancer in EMT (64,65).

The transcriptional repressors of E-cadherin can be regulated by hypoxia in lung cancer (17). Hypoxia-inducible factor-1 (HIF-1), a major regulator of the cellular response to hypoxia, has been shown to regulate vimentin gene expression (66). Therefore, vimentin transcriptional regulation by HIF-1 may be a potential driver of EMT in lung cancer (42).

The expression of CSC-associated transcription factors could provide prognostic information of lung cancers (11). Among them, Bmi-1 has been shown to sustain stem cell properties in normal and cancerous lung tissues (67,68). An increased expression of Oct4 and Nanog was found to be associated with a worse prognosis in lung adenocarcinoma patients (69). Thyroid transcription factor-1 (TTF-1) is a transcription factor that is expressed in ~75% of lung

adenocarcinomas (3). Loss of expression of TTF-1 was observed to facilitate the generation of EMT by tumor cells resulting in a worse prognosis of patients.

Mani *et al* (32) demonstrated that immortalized human mammary epithelial cells induced to undergo EMT acquired expression of stem cell markers. Differentiated mammary epithelial cells that had undergone EMT via TGF-β1 treatment or ectopic overexpression of Snail or Twist gave rise to $CD44^+CD24^-$ cells with tumor-initiating capacity (17). More recently, LBX1, which directs expression of Snail, Zeb1 and Zeb2, was also noted to expand the $CD44^+CD24^-$ CSC subpopulation and to morphologically transform mammary epithelial cells (70).

4. Epigenetics and regulatory transcription factors

Recently, researchers have focused their attention on the roles of epigenetic regulation in the EMT process due to the hypothesis that epigenetic alterations have important influences on tumorigenesis (71). Histone acetylation, microRNA (miRNA), and DNA methylation refer to three major epigenetic modifications contributing to tumorigenesis including EMT and cancer metastasis (72,73).

Aberrations of any of the three major histone proteins, HATs, HDACs and histone readers, have been demonstrated to be closely correlated with lung cancer (74). The microenvironment, such as hypoxia, is demonstrated to be correlated with histone acetylation which consequently affects the EMT process (74). Increasing evidence suggests that histone acetylation/deacetylation may regulate E-cadherin during EMT in several types of cancers, including lung cancer (75). The understanding of the mechanisms of histone acetylation and its interaction with other epigenetic modifications in EMT may provide the means by which to develop potential therapeutic strategies with higher efficiency and fewer side-effects (74).

miRNAs are a class of small non-coding RNAs that negatively regulate gene expression by binding to homologous regions in target mRNAs inducing mRNA degradation (76,77). miRNAs play important roles in essential cellular processes including cell growth, differentiation, apoptosis and immune response (17). miRNAs serve as key administrators of post-transcriptional regulation and participate in EMT (78). Aberrant expression of various miRNAs is related to tumor growth and metastasis (79,80).

One of the first characterized miRNA families relevant in carcinogenesis was the miR-17-92 cluster (81). It has been demonstrated that miR-17-92 cluster expression is upregulated by the proto-oncogene, c-myc, which itself is commonly dysregulated in human malignancies (82). Among other c-myc-induced miRNAs are miR-221 and miR-222, which target proteins involved in cell cycle arrest (82). miR-9 suppresses E-cadherin expression and promotes metastasis (17). Overall, the c-myc-induced miRNA network is reported to be directly related to tumor aggressiveness in various types of cancers (83).

miR-10b initiates the development of distant metastasis (84). miR-21 and miR-31 have been identified as TGF-β-dependent positive regulators of tumor cell migration, invasion and metastasis (17). High levels of miR-21 have been found in lung cancer, and its target network includes tumor suppressive components of the p53, TGF-β and mitochondrial apoptosis pathways (85).

miR-200 family members are downregulated during the EMT process (86,87), which in turn leads to upregulated expression of several key target genes (88). The most notable example being the regulation of Zeb1/2 by the miR-200 family, where loss of miR-200 leads to EMT (78,89,90). Other miRNAs that regulate Zeb1/2 include miR-205 and miR-192/215 (89,91). miRNAs that regulate Snail1/2 include miR-1, miR-29b, miR-30c, miR-34 and miR-203 (92).

The role of EMT mediators in the regulation of miRNAs is just beginning to be revealed (17). Transcriptional repressors, such as Snail, Slug and Twist that are induced by inflammation are involved in this regulation (17). For example, Snail is able to upregulate miR-661 increasing the metastatic potential of breast cancer cells (93). Twist upregulates a positive regulator of cancer cell migration and invasion.

In recent years, miRNA studies have demonstrated that miRNAs implicated in EMT may serve as diagnostic and prognostic markers for various types of cancer (94). Further studies are needed to define the detailed mechanisms to verify the role of individual miRNAs in lung cancer. This may allow the development of novel therapeutic strategies targeting oncogenic miRNAs in lung cancer.

5. Invasion and metastasis

EMT is largely thought to play an important role in invasion and metastasis. EMT may enable cancer cells to lose their cell polarity and cell-cell adhesive interactions, allowing the cells to escape from the primary tumor (95). Cancer cells, that have acquired mesenchymal characteristics, can more effectively invade surrounding tissues and migrate to distant sites. Since tumor metastasis is the main obstacle for long-term survival, identification of molecular markers related to metastasis may predict the prognosis of patients with lung cancer (3). Increased E-cadherin expression was found to markedly decreased the invasion/migration of tumor cells (96). In contrast, the upregulation of N-cadherin expression is linked to the metastasis of NSCLC (97).

The association between EMT and metastasis comes from clinical observations that distant metastasis derived from a variety of primary carcinomas resemble an epithelial phenotype (98). For example, metastases in distal organs derived from a variety of primary types of tumors exhibit overt epithelial phenotypes (99,100). These observations raise the possibility that tumor cells may disseminate without switching to a mesenchymal phenotype, thereby providing controversy to the requirement of EMT for metastasis formation (98). In contrast, if cancer cells must undergo EMT to disseminate, an important question is why the resulting metastases closely resemble, at the histopathologic level, the primary carcinomas from which they have originated (98). This question has led to the possibility that the disseminated mesenchymal tumor cells recruited to target organs may undergo a reverse phenotypic transition from a mesenchymal back to an epithelial phenotype by a process called mesenchymal-to-epithelial transition (MET) (98). Xue *et al* (101) reported that disseminated breast tumor cells expressed mesenchymal marker Fsp-1, suggesting that EMT had occurred, which could shift back to

an Fsp-1-negative phenotype, suggesting MET. This finding suggests that cancer cells may undergo MET in the secondary metastatic organ (98). E-cadherin was expressed at a higher level in metastatic lesions in the brain from the primary lung cancer (100). These results indicate that EMT occurs during lung carcinogenesis as well as the inverse process MET in metastatic sites (74).

Numerous strategies are being explored to develop non-invasive methods by which to detect cancer (17). These include investigations into the detection of circulating cancer cells, as well as identifying biomarkers in bronchial, oral or nasal samples (17). Profiling serum-based miRNAs is also under investigation and shows promise in identifying cancer patients vs. non-cancer individuals (102,103). miRNAs, particularly the miR-200 family, have been implicated in EMT/MET transitions in cancer (104). miR-200c was found to inhibit EMT and induce an epithelial phenotype (105). In lung cancer, the number of circulating tumor cells (CTCs) expressing epithelial marker EpCAM was found to be lower compared with the number in other solid tumors (106). However, when CTC isolation is not based on epithelial markers, the CTC numbers are similar to those of other solid tumors and have strong prognostic value (107). These data suggest that lung cancer CTCs lose their epithelial characteristics having undergone EMT (108).

6. Future target therapy and conclusion

EMT has also been related to therapy resistance in cancer, with both preclinical and clinical evidence (95). Therapeutic refractory lung cancer cells frequently reveal an EMT phenotype, and signaling to block EMT has been shown to enhance chemotherapy sensitivity (109,110). Taken together, EMT, metastasis and drug resistance are intertwined in lung cancer, and lead to aggressiveness and poor prognosis (51).

Although the underlying mechanisms have been studied for many years, the overall survival rates have not been significantly improved for patients receiving targeted therapy as compared with chemotherapy (111,112). Currently, the major therapeutic obstacles are tumor recurrence and metastasis even after surgical resection, which are the main causes of mortality (74) in lung cancer patients. Studies concerning the molecular biology of EMT have elucidated the processes of invasion and metastasis, and it is expected that these basic biological findings can be eventually translated into new therapeutic approaches (95).

Receptor-specific approaches such as monoclonal antibodies or siRNAs directed against Notch may be useful in reducing the tumorigenicity and invasiveness of lung cancer (113). For instance, nanoparticle (NP) technology has been applied to deliver specific siRNAs to knock down Notch1 to arrest tumor growth and reverse EMT by the upregulation of miR-200 and downregulation of the transcription factors ZEB1, ZEB2, Snail and Slug (114).

Intermediate filaments (IFs) are an attractive potential therapeutic target for lung cancer, due to their involvement in cellular motility, transcriptional regulation, and association with EMT and tumor metastasis (42). Vimentin may be a key regulator of several tumorigenic pathways, as it forms a complex that may prevent the dephosphorylation of proteins in the complex, inhibiting antitumor activity within tumor cells (42). Furthermore, inhibition of vimentin expression by RNA interference has been shown to reduce metastatic cell invasiveness and decrease tumor volume (115).

As Wnt signaling pathways have been shown to be important in the pathogenesis of lung cancer (116), they could serve as another promising therapeutic target. At present, there are multiple therapeutic approaches targeting Wnt signaling in lung cancer which may be applied in the near future (117,118).

Since CSCs share several stem-like characteristics with normal stem cells, targeted CSC therapies should be designed to preserve normal stem cells and to 'hit' only CSC-specific signaling pathways (119). The final aim is to develop a CSC-targeted therapy that will result in the complete elimination of CSCs. Presumably, this could be achieved through the disruption of signaling pathways that control the self-renewal, proliferation and differentiation of CSCs (11). Since most studies on the therapeutic efficacy of CSC targeting drugs are still in their early phases, more information must be gathered to verify the clinical importance of these drugs (11).

In conclusion, much research has highlighted the involvement of EMT in lung cancer. The precise clinical importance of the association of EMT and tumor invasion/metastasis, chemoresistance of tumor cells, *de novo* generation of CSCs, and tumor microenvironment remains to be determined. However, the development of drugs that target chemical mediators known to promote EMT suggest that regulation of EMT processes in the clinical setting may be possible. We anticipate the identification of novel molecular targets to facilitate the development of therapeutic agents for lung cancer as the relationships between EMT, tumor microenvironment, and CSCs are further explored in the near future.

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